International Journal of Advanced Research in Science, Engineering and Technology

ISSN: 2350-0328

Vol. 12, Special Issue, December 2025

National Conference on Earth, Elements and Energy: Interdisciplinary Perspectives (NC3EIP–2025)

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# A concise review for the synthesis of 2-azetidinone derivatives

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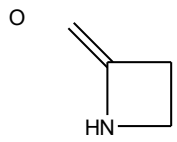
**ABSTRACT:** 2-azetidinone a heterocyclic molecule is a very versatile and special molecule for its wide range of application. One of the all-round branches of chemistry is the heterocyclic chemistry as the heterocyclic compounds has its medicinal, pharmaceutical, pharmacological, agricultural and many such application. 2-azetidinone also known as β-lactam is one of such versatile heterocyclic four membered cyclic molecules with nitrogen as a heteroatom. The first ever made antibiotic penicillin also contained a 2-azetidinone ring in it, hence the day forward the derivatives of 2-azetidinone are being studied. For instance, anti-inflammatory, antibiotic, anticancer, ant diabetic, anti-tubercular, anti-analgesic, antiviral, and many such bioactivities are exhibited by the 2-azetidinone derivatives. For these reasons this versatile molecule holds a special place as a heterocyclic molecule hence the need for its future study. The overview of this molecule is made in order to further study the derivatives of 2-azetidinone for its synthesis and biological activities.

**KEYWORDS:** 2-azetidinone, bioactivities, heterocyclic.

## I.INTRODUCTION

2-azetidione a heterocyclic compound is very well known to organic chemists due to its versatile nature. Heterocyclic compounds are famous due to its bioactivities as infectious diseases are one of the causes of deaths in human beings. To tackle them antibiotics synthesis are being done by many organic chemists. Penicillin the first ever prepared antibiotic contains a 2-azetidinone also known as β-lactam ring is present in it. β-lactam or 2-azetidinone are the names used vice versa because the carbonyl group is present on the second (β or 2) position from nitrogen which is the hetero atom in the four membered heterocyclic ring of the 2-azetidinone.




2-Azetidinone

β-lactam ring is present in many other medicines, drugs, agricultural insecticides and pesticides. Hence, the need to investigate the synthesis, chemistry and biology of β-lactam ring and its derivatives. Unlike penicillin β-lactam ring is also present in many other antibiotics like ampicillin, nocardicin, clavam, cephalosporins, carbapenem, etc. Due to this reason 2-azetidione and its derivatives synthesis is very popular in organic chemists.

In this review paper we have focused on the synthesis of 2-azetidinone derivitives and collected and piles up the data for the synthesis of 2-azetidinone derivatives for various research journals, publications and articles European chemical society, international journal of health science, educational administration theory and practice, Zanco journal of pure and applied science, Elsevier, Journal of advanced scientific research, J. Chem. Sci., MDPI, European journal of medicinal chemistry, science direct, international jopurnal of bioscience and biochemistry , advanced journal of chemistry and Indones. J. Chem.

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## II. RELATED WORK

Synthesis of 2-azetidinone is done all over the world due to its applications in pharmaceutical, agricultural, medicinal and many such many such applications. This review helps to understand the synthesis of 2-azetidinone using different starting materials and conditions needed to synthesize it.

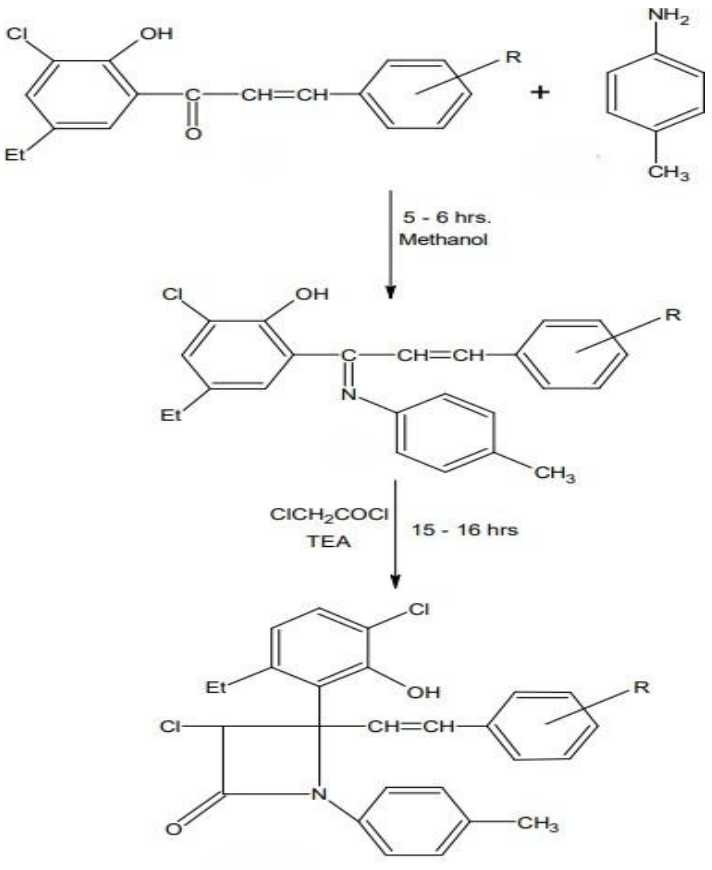
## III.SIGNIFICANCE

It will help researchers to understand many aspects for the synthesis of 2-azetidinones and its derivatives. Also, it will help to know that there is no repetition of the synthesis work. Help in selecting suitable method to prepare the derivatives of 2-azetidinone.

## IV.METHODOLOGY

***Synthesis of 2- azetidinone:***

Chalcone and p-toluene were used as the starting materials for the synthesis of 2-azetidinone derivatives by K. Vashi *et al* [1]. Both were mixed with methanol and refluxed for about 6 hours and the product formed was the Schiff base. This Schiff base was then mixed with benzene and then triethyl amine and chloroacetyl chloride was added drop wise and then was refluxed the product so formed after the refluxing is the 2-azetidinone.




R = p-H, p-Cl, 2,4-$(Cl)_2$, o-OH, p-OH, p-$CH_3$, m-$NO_2$, o-$OCH_3$, p-$OCH_3$, p-$N(CH_3)_2$.

Schiff base was first synthesized using anisidine dissoloved in ethanol and adding few drops of glacial acetic acid after this aromatic aldehyde was added to the mixture and then refluxed for about five hours by S. Jubie *et al* [2]. The

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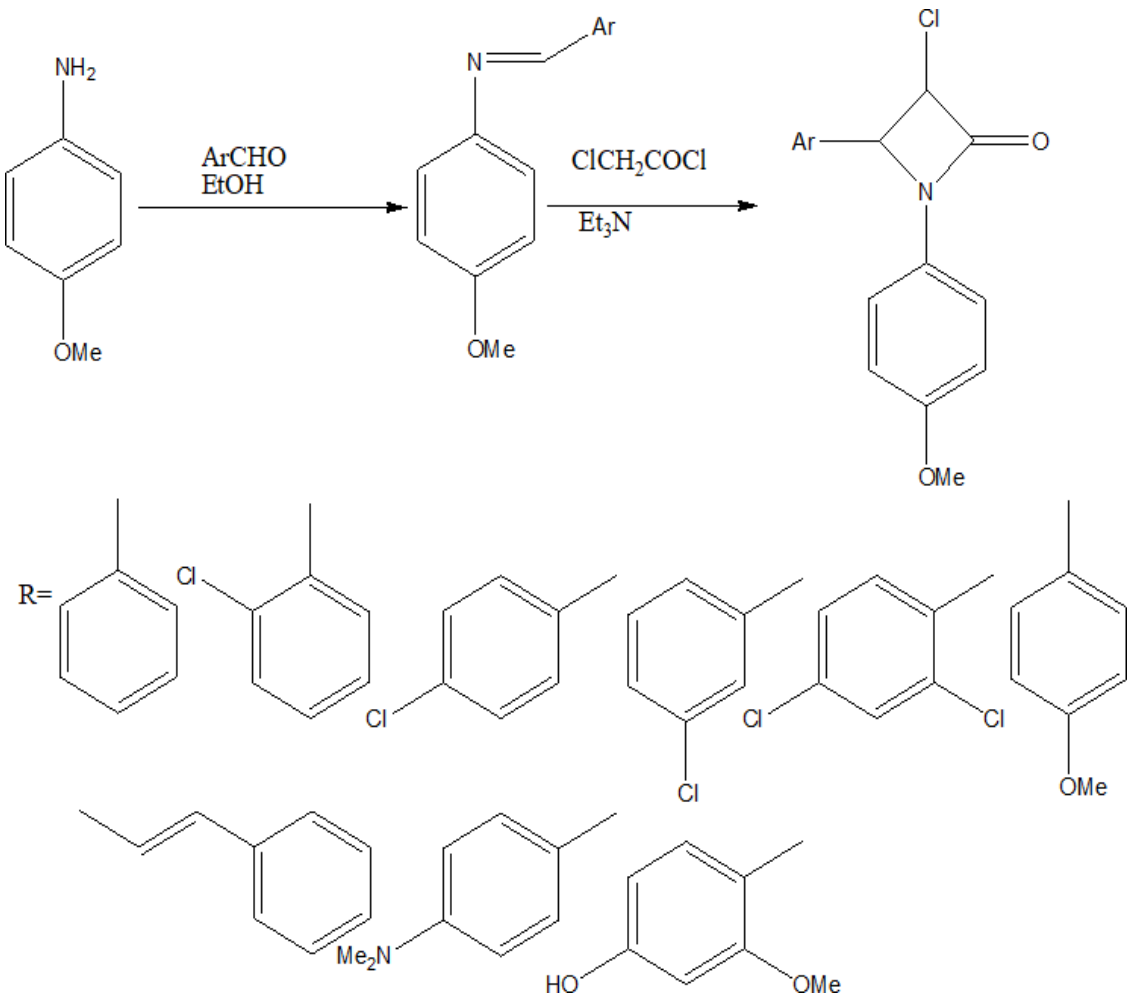
Schiff base so formed was put in dioxin and was then added with triethylamine and chloroacetylchloride was added gradually and slowly and then stirred and refluxed to synthesize 2-azetdidnones.




Synthesis of 2-azetidinones was done by D. Kumar *et al* [3] for testing its bioactivities. They reacted an acethydrazide with aromatic aldehyde in ethanol and refluxed for 2 hours to yield Schiff base. The Schiff base is then treated with trietyhyamine and chloroacetyl chloride in dioxane with constant stirring for 3 hours to yield 2-azetidinone.

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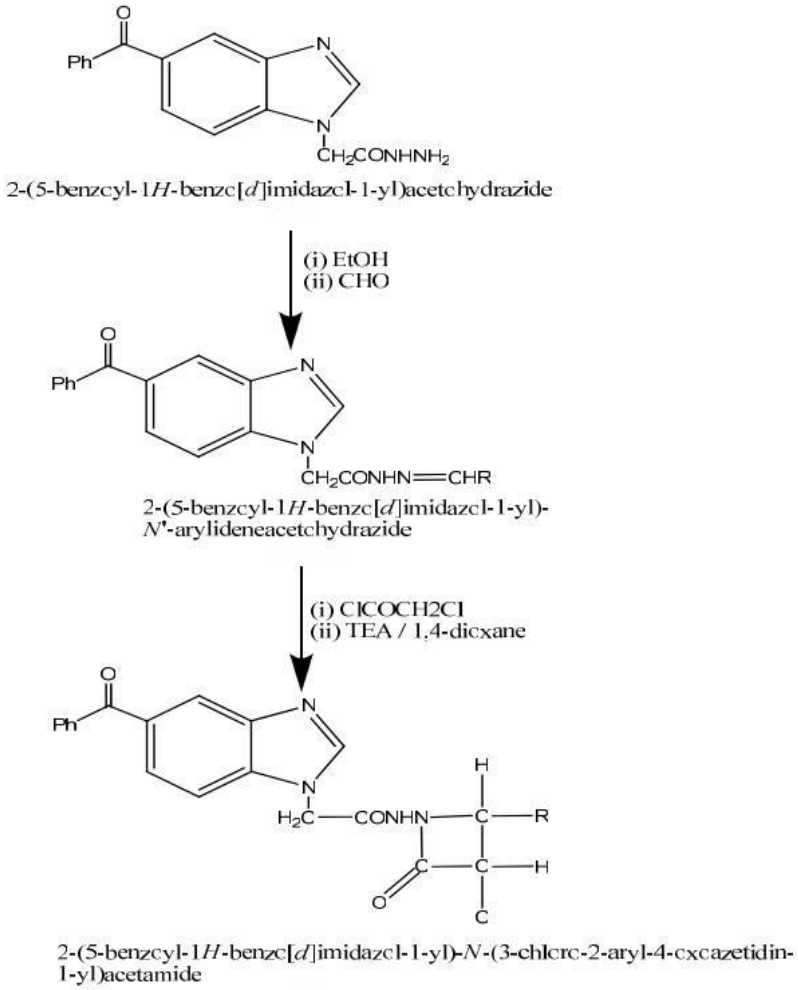


Scheme - 1

Where, R = (a) $C_6H_5$ (b) 4-$OCH_3$-$C_6H_4$ (c) 4-OH-$C_6H_4$
(d) 2-OH-$C_6H_4$ (e) 4-$CH_3$-$C_6H_4$ (f) 3,4-$CH_2O_2$-$C_6H_4$
(g) 4-OH-3-$OCH_3$-$C_6H_3$ (h) 3,4-$C_2H_5$-$C_6H_4$

Phenothiazine reaction with bromo chloro propane at room temperature to form a phenothiazine compound which was then treated with urea to yield a phenothiazine substituted urea. This compound is then further reacted with substituded aldehyde to form Schiff base. The Schiff base is then reacted with chloroacetyl chloride in the presence of triethyl amine to synthesize 2-azetidinone by R. Sharma *et al* [4].

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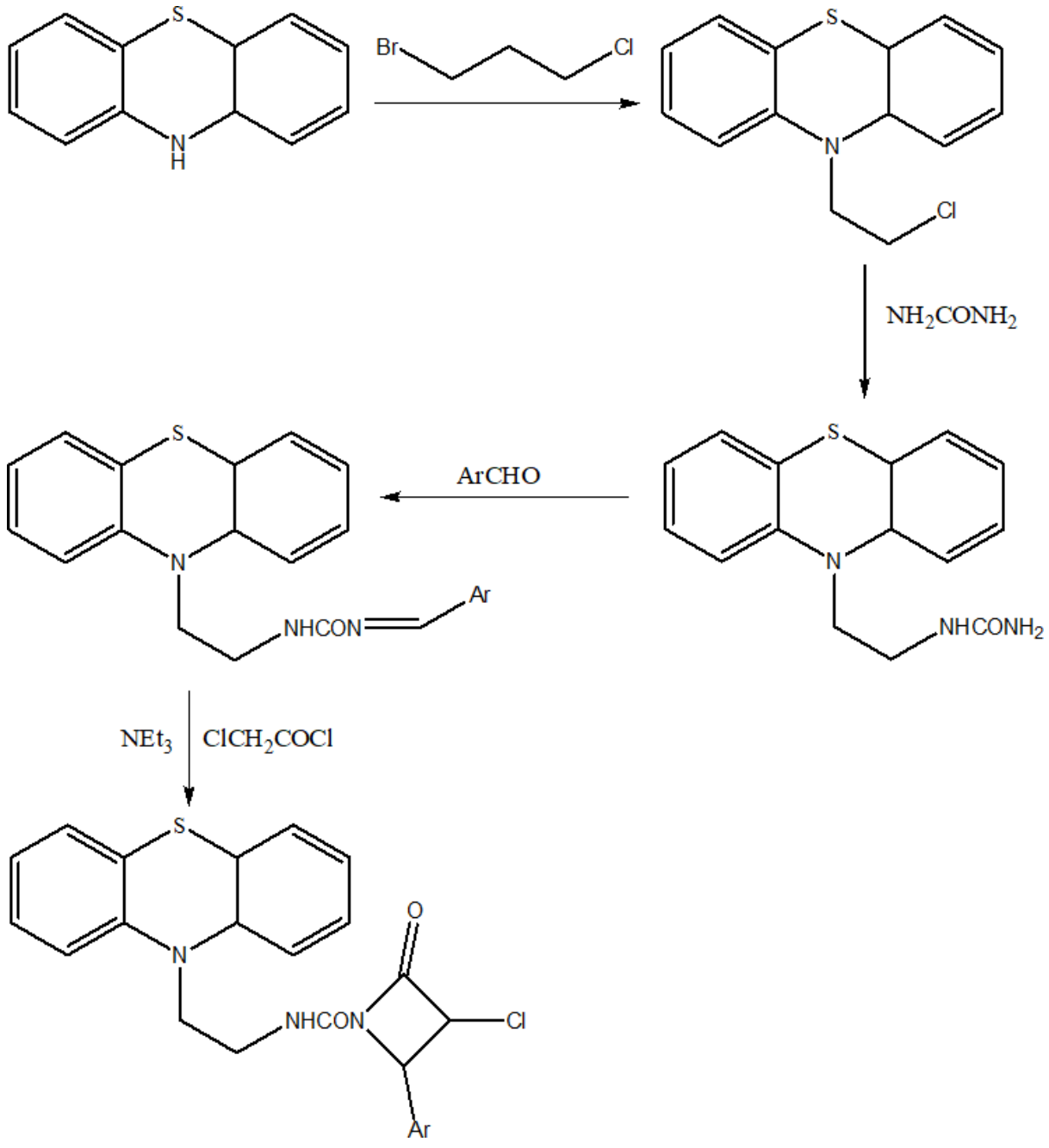


Ar = substituted (R) phenyl ring where R= $NO_2$, Cl, Br, OH, $OCH_3$ > H, $CH_3$.

2-azetidinone derivatives were synthesized by R. M. Sulthana *et al* [5] using carboxylic acid as a starting material. The carboxylic acid was mixed with ethanol and conc. Sulphuric acid and then refluxed to yield an ester. This ester is then reacted with hydrazine in the presence of ethanol to form an acid hydrazide which is further reacted with aldehyde to give the Schiff base. The Schiff base is then reacted with triethylamine and chloroacetyl chloride to give 2-azetidinone.

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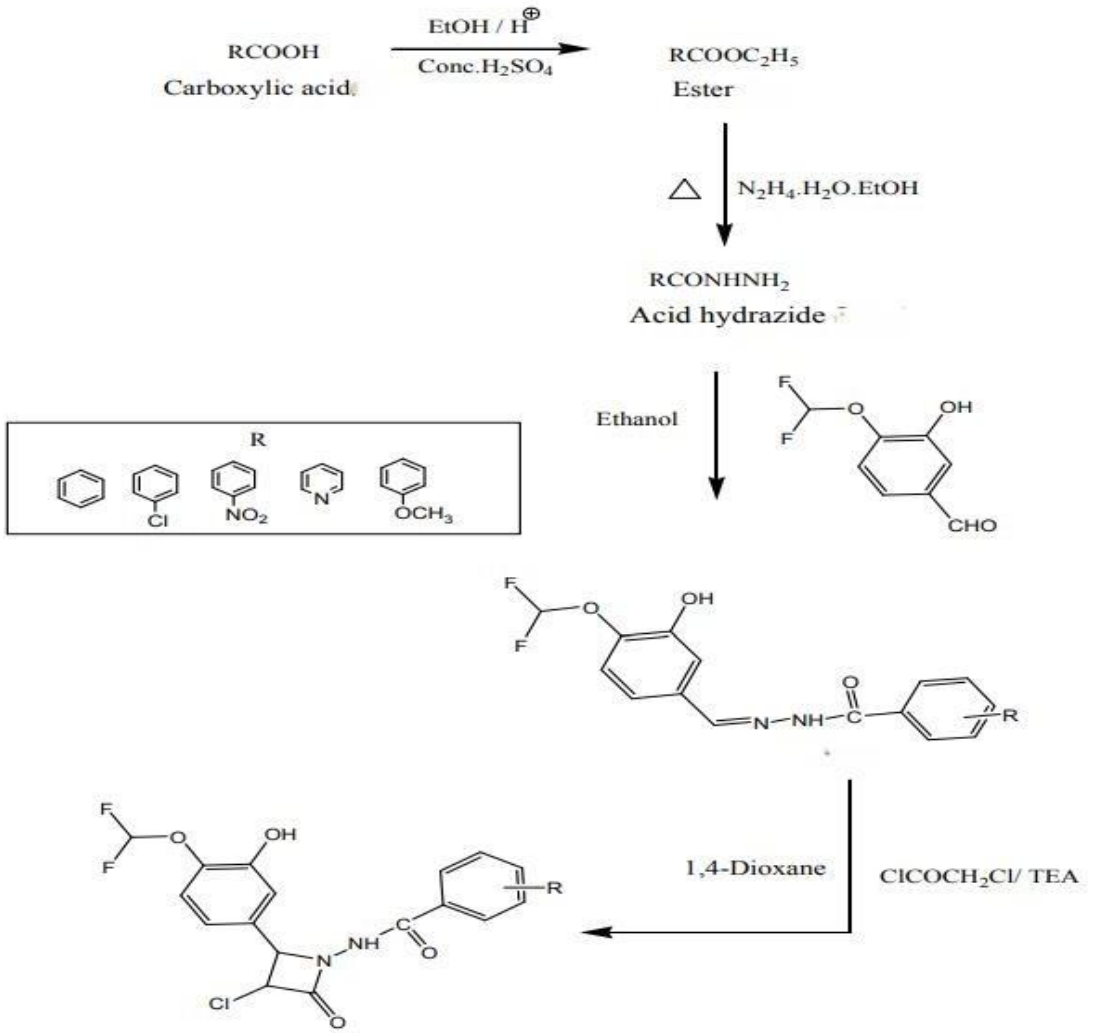


First esterification of pyrizine dicarboxylic acid was done with EtOH to form diester compound by A. N. Ayyash *et al* [6]. This diester is then refluxed with hydrazide to form dicarbohydrazide which is then reacted with the pyridine-2- carbaldehyde derivatives in acidic medium along with ethanol to synthesize Schiff base. The formed Schiff base is mixed with triethylamine and DMF in two different containers along with the gradual addition of chloroacetylchloride in the first and dichloroacetylchloride in the second container is to yield 2-azetidinone derivatives.

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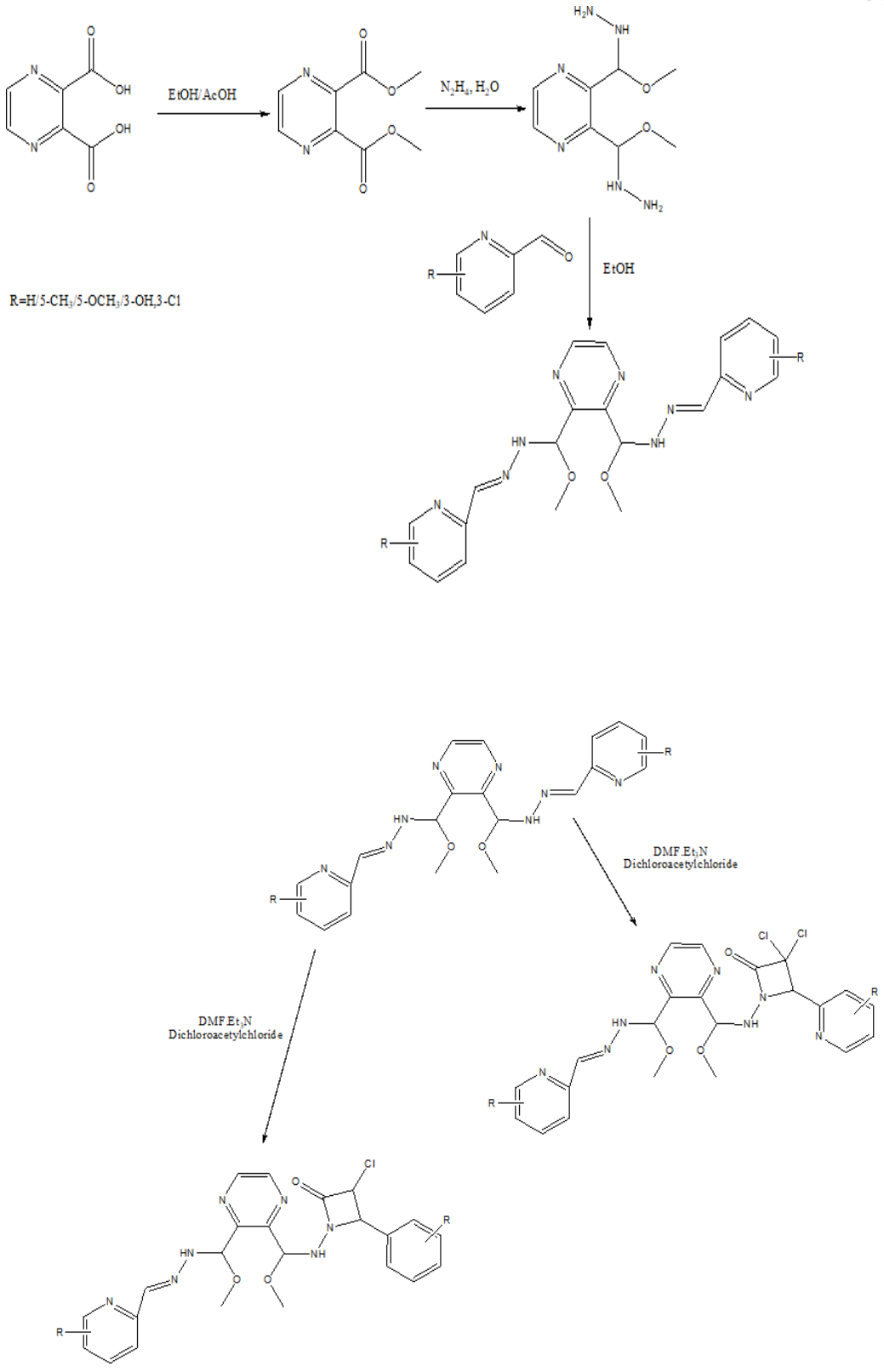

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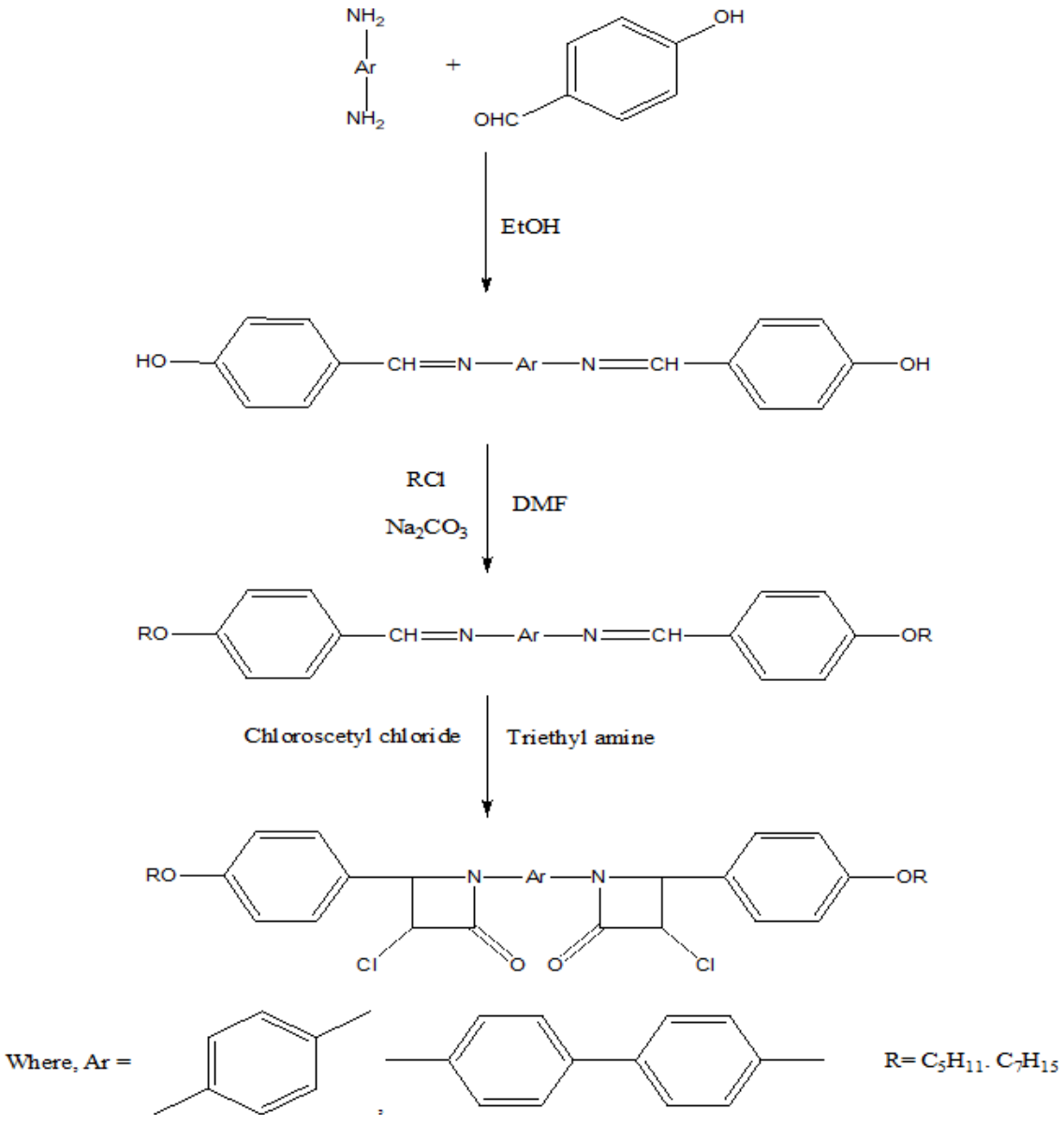
M. M. Aftan *et al* [7] synthesized 2-azetitdinone derivatives by first making many Schiff's bases using diamine dissolved in ethyl alcohol with a few drops of glacial acetic acid and then adding p-hydroxy benzaldehyde to get Schiff's bases after refluxing. These Schiff's bases were then dissolved in DMF and reacted with sodium carbonate and alkyl chloride to get the desired ethers. These ethers were then reacted with dry dioxane, triethylamine and monochloacetyl chloride to get the 2-azetidinone derivatives.




Synthesis of 2-azetidinone from substituted anliline by treating it with AcOh and Ac2O to give acetanilide was done by K. Govondarao *et al* [8]. Then this acetanilide is the treated with POCl3 in DMF to yield a quinoline then again reacted with aminoacetophenone to synthesize the Schiff base. This Schiff base is then mixed with triethylamine and chloroacetyle chloride which is added drop wise to yield the 2-azetidinone derivatives.

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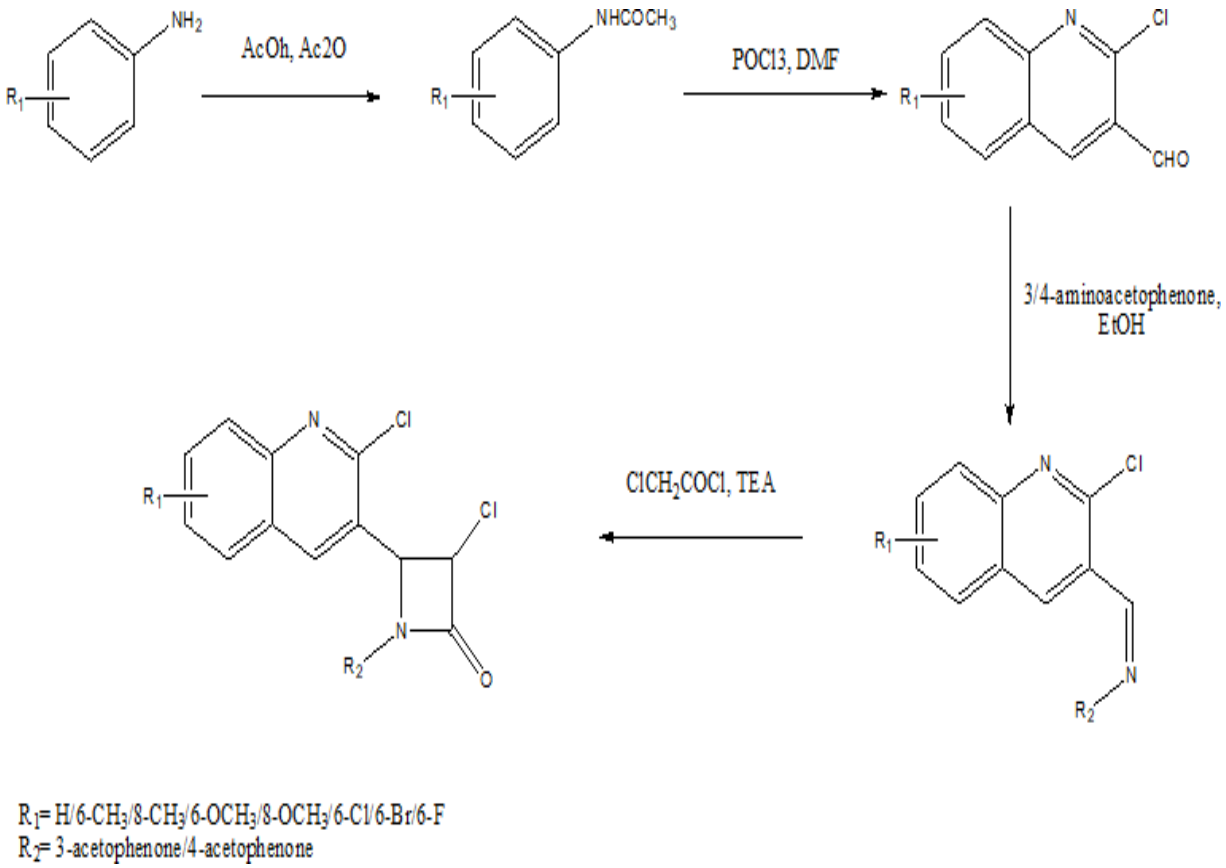


$R_1$= H/6-$CH_3$/8-$CH_3$/6-$OCH_3$/8-$OCH_3$/6-Cl/6-Br/6-F
$R_2$= 3-acetophenone/4-acetophenone

Z. K. Al-Khazragie *et al* [9] synthesized substituted amides by first refluxing with 2-chloroquinoline-3-carbaldehyde with $Na_2NH_3$, PTSA in ethanol then a catalytic amount of concentrated $H_2SO_4$ was added to the solution and again refluxed with sulfonamide derivatives to produce substituted amine. These substituted amines are then mixed with triethyl amine and dissolved in 1, 4, - dioxane cooled and stirred. To this cooled stirred solution chloroacetyl chloride is added and stirred for 8 hours and kept at room temperature and filtered to get the derivatives of 2-azetidinone.

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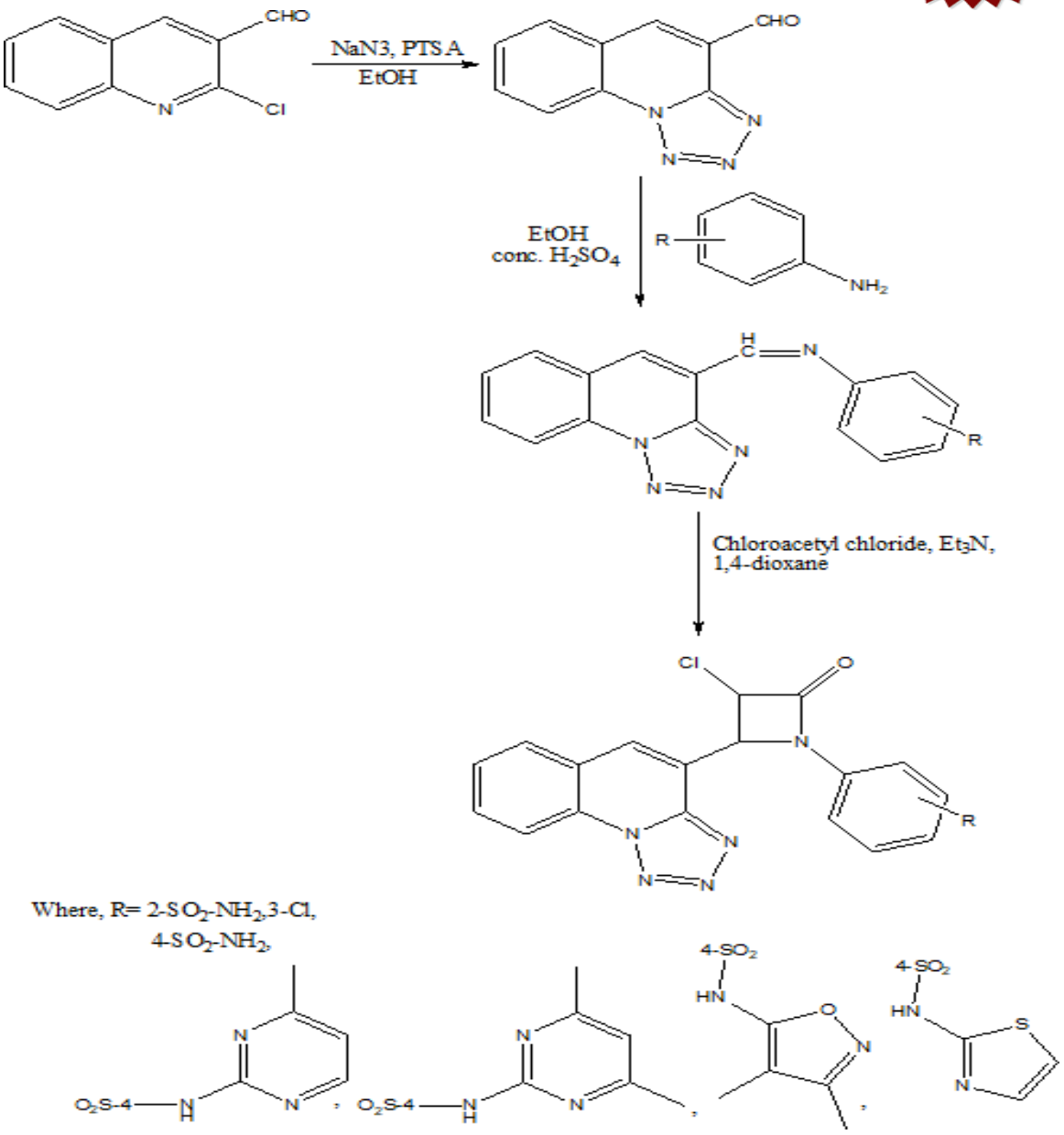


R. V. Kusurkar *et al* [10] began with the synthesis of 2-aminophenyl acetic acid by reduction with 2,4- nitrophenyl acetic acid using ammonium formate by using H2PdC. Then the esterification of 4-aminophenyl acetic acid is done with SOCl2 and anhydrous MeOH under reflux condition to yield methyl-4-aminophenyl acetate. This acetate is then reacted with 2-bromopyridine-4-carboxylic acid in the presence of HATU and DIPAA in DMF to give compound pyridine substituted benzoate which is then treated by hydrazine hydrate in MeOH at room temperature undergoing condensation to form a isonicotinamide. This isonicotinamide is then reacted with substituted aldehydes in acetic acid or sulphuric acid acting as a catalyst to yield hydrazine hydrazones derivatives. These are then irradiated with in microwave at 250W with ethanol and acetic anhydride to yield a Schiff's base which is further treated with anhydrous DCM, choloracetyl chloride and triethyl amine to yield the derivatives of 2-azetidinones.

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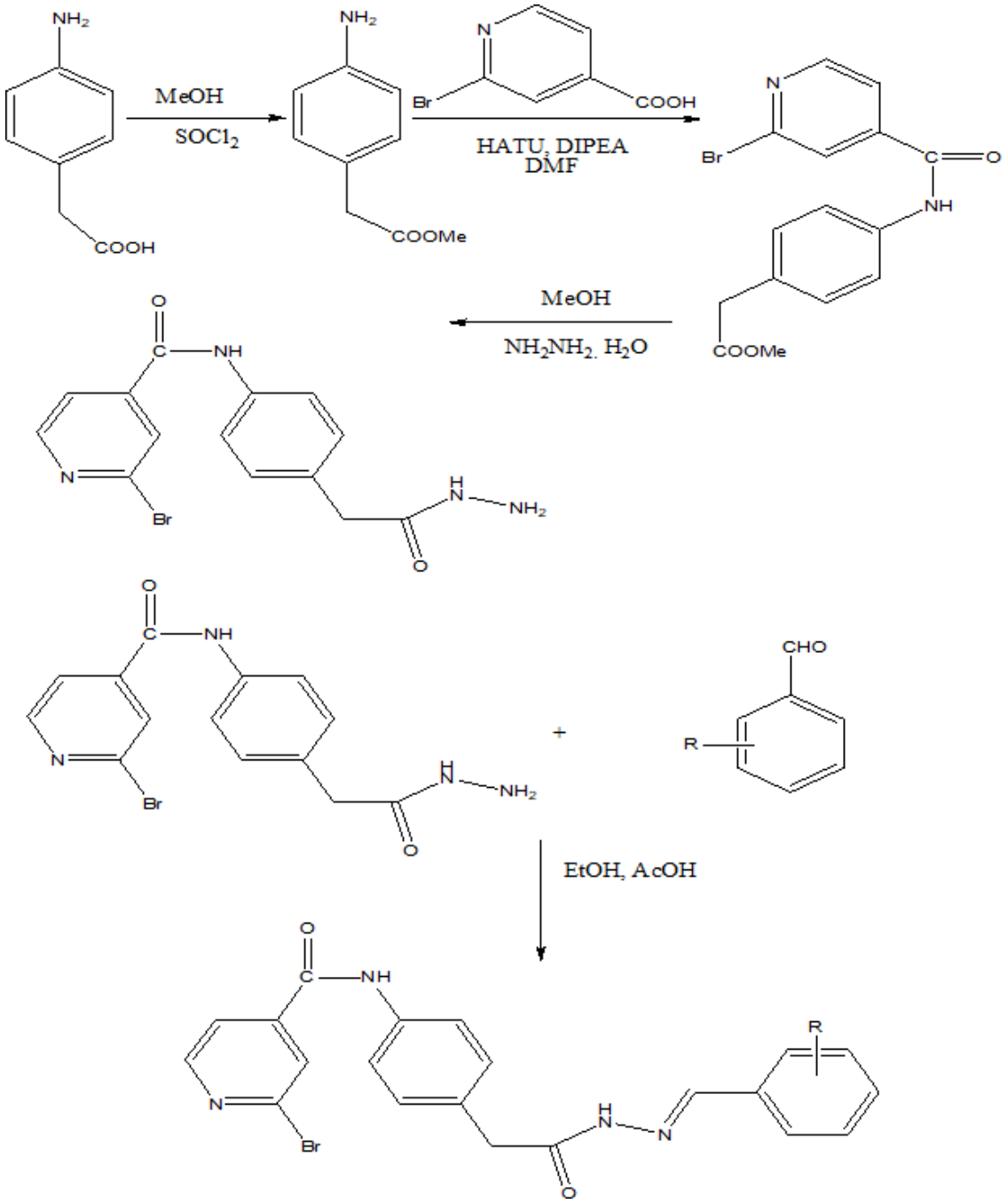

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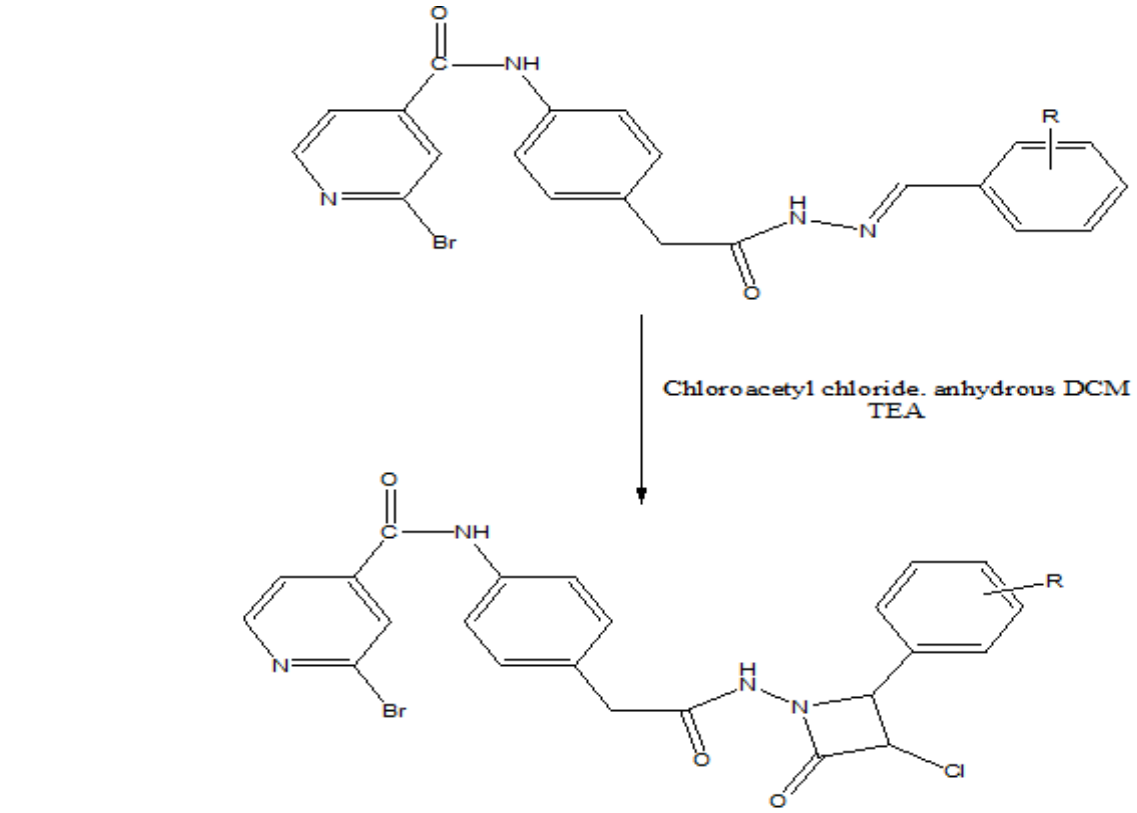
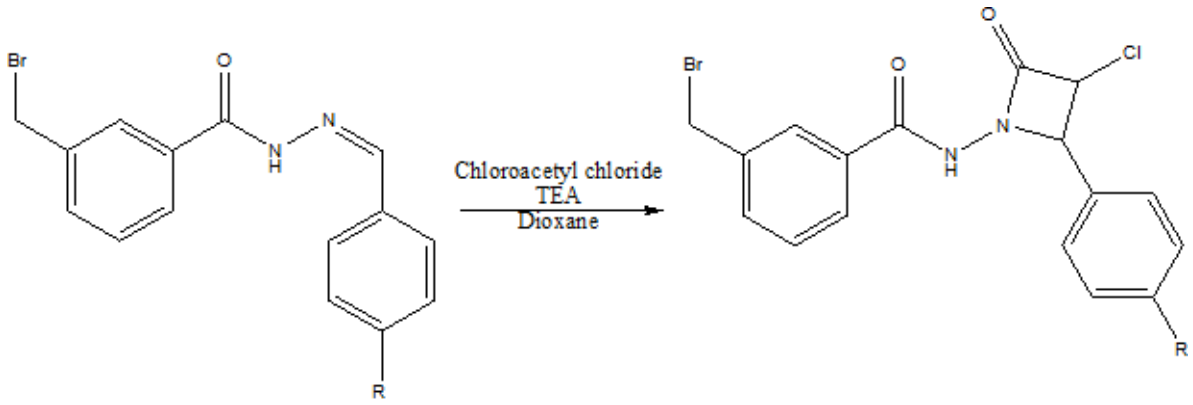



Where, R= a) 4-Br, b)3-F, c) 2-C,1 d)2-Br, e)4-OH, 3-$OCH_3$ , f)4-F, g) 4-$NO_2$, h)4-Cl, i)3-CN, j)2,4-F

S. E. Ahmed *et al* [11] synthesized 2-azetidinone using a hydrazone. The hydrazones were first dissolved in 1,4- dioxane the triethylamine was added to this solution and is then placed in an ice bath with constant stirring with the addition of chloroacetyl chloride drop wise gradually with a time period of ten minutes. Let the mixture for constant stirring for about eight hours and the precipitated and filtered. Dried and recrystallized to the pure 2-azetidinone derivatives.




R= Br, Cl, $NO_2$, $CH_3$, OH

G. Subramanian *et al* [12] used naphthalene-1-yl acetic acid to synthesize 2-azetidinone. First this acetic acid was mixed with ethanol with drop wise addition of sulfuric acid and refluxed to give the acetate. The acetate is then dissolved in methanol and reacted with hydrazine to yield aceto hydrazide which is then reacted with aromatic aldehyde in

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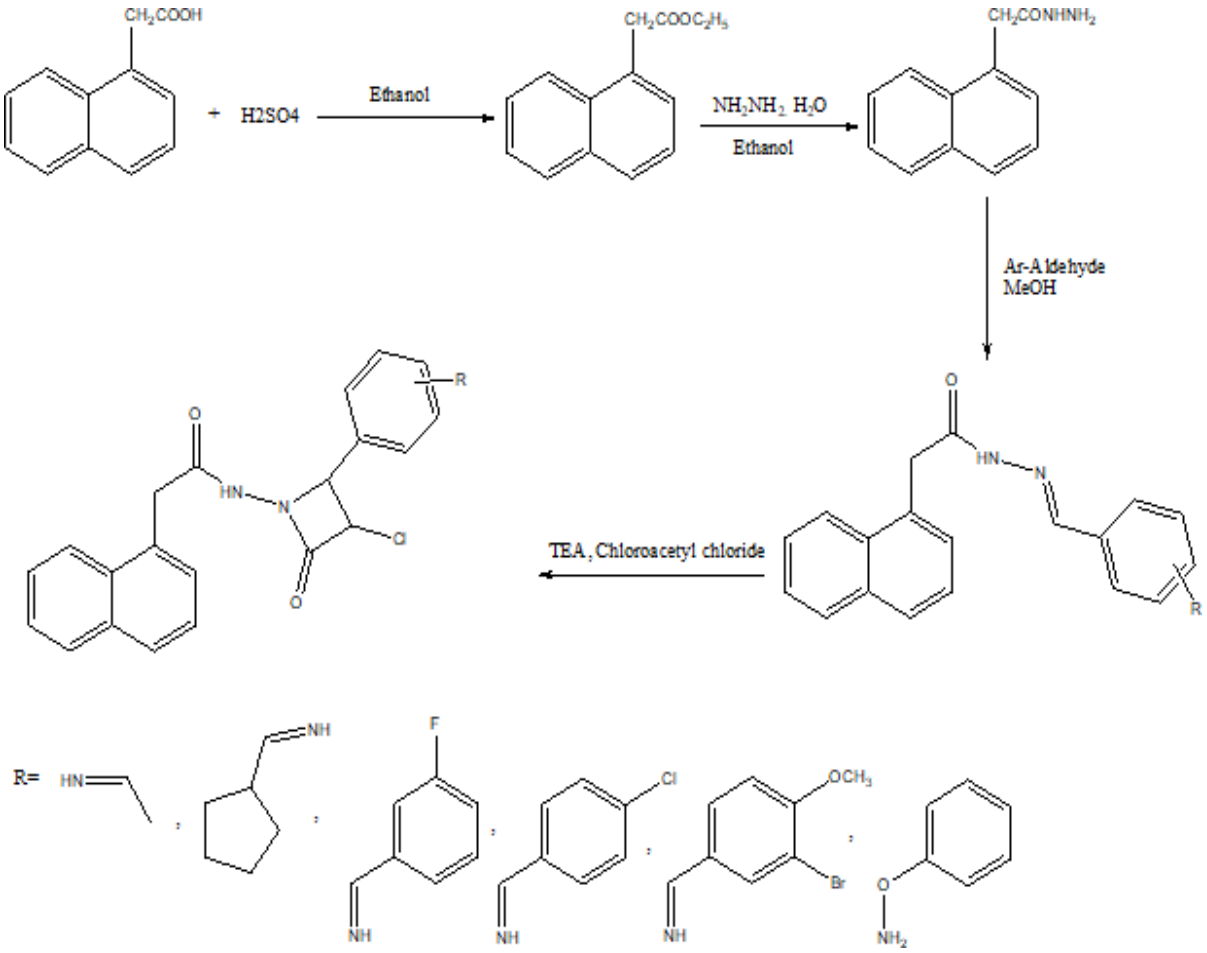
methanol to give a Schiff base. This Schiff base is then reacted with triethylamine and chloroacetylchloride drop wise addition to yield 2-azetidinone.




H. C. Sakarya *et al* [13] first prepared schiffs base by refluxing the mixture of 6-ethoxy-2-aminobenzothiazole and para-methyl benzaldehyde in dichloromethane for 6 hours to yield the precipitate of schiffs base. Chloroacetyl chloride is then added drop by drop in the mixture of dichloromethane and triethyl amine solution within the time interval of thirty minutes at cold condition and stirred. To this cold well-stirred solution Schiff base is added and stirred for nine hours and kept at room temperature for 6 hours. This reaction mixture was then extracted using NaHCO3, HCl, and brine and then purified by column chromatography over silica gel to get 2-Azetidinones.

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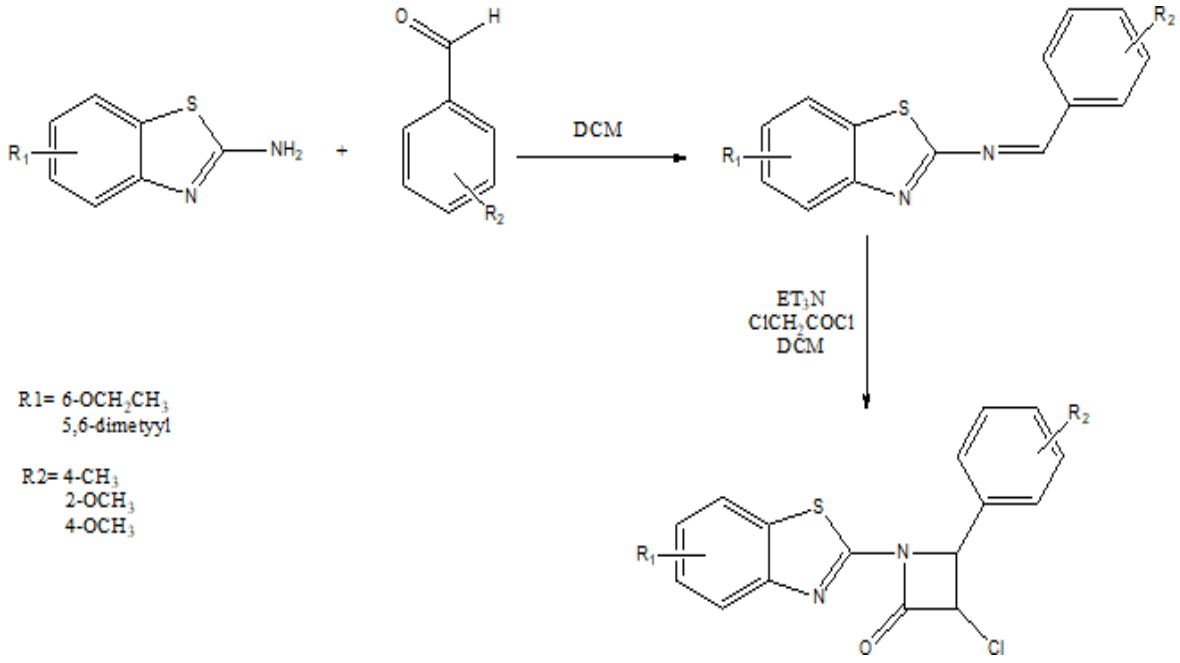
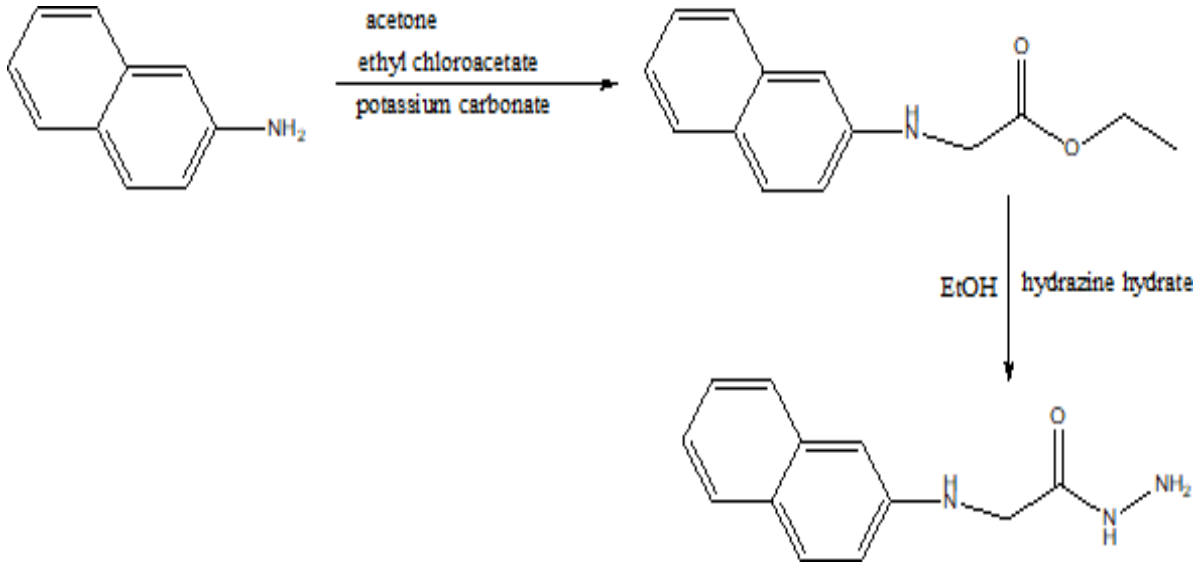



G. Kumar *et al* [14] first mixed naphthaline-2-amine with acetone and then ethyl chloroacetate was added with a pinch of potassium carbonate and stirred for 30 minutes and refluxed to yield acetohydrazide. This acetohydrazide is then mixed with ethyl alcohol and then hydrazine hydrate is slowly added to it with shaking to produce acetohydrazide. The so formed acetohydrazide is then mixed with arylaldehyde and few drops of acetic acid are added to it contained in ethyl alcohol and then refluxed to yield Schiff's base. This Schiff base is then mixed with triethyl amine and chloroacetyl chloride is then added drop wise to yield 2-azetidinone derivatives.



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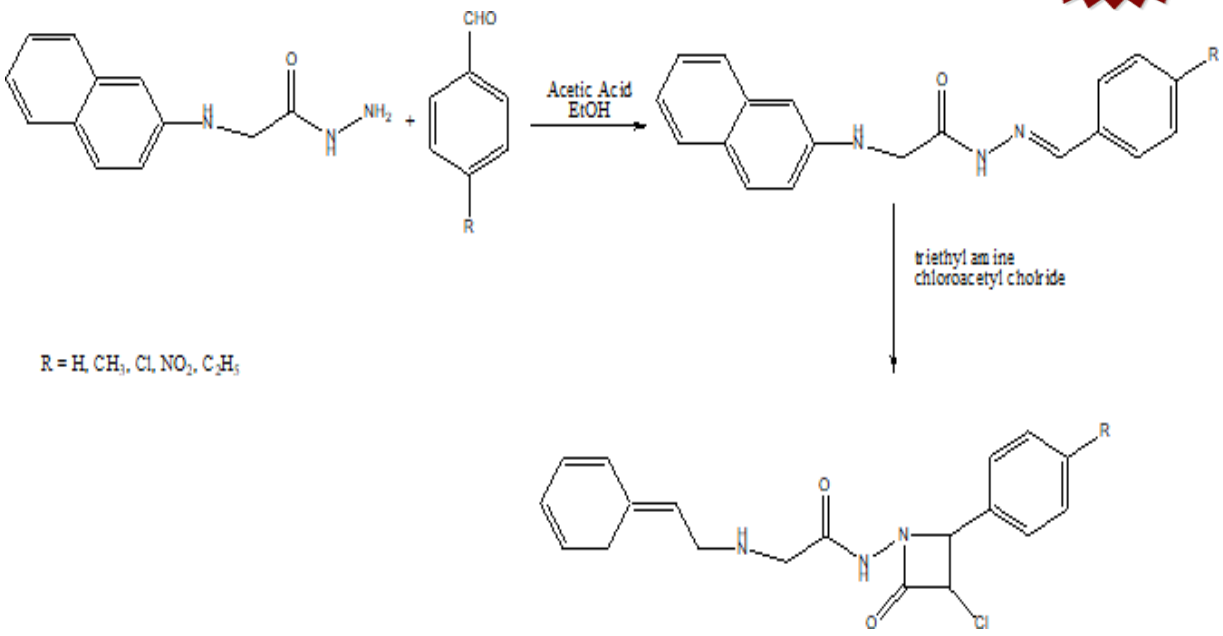
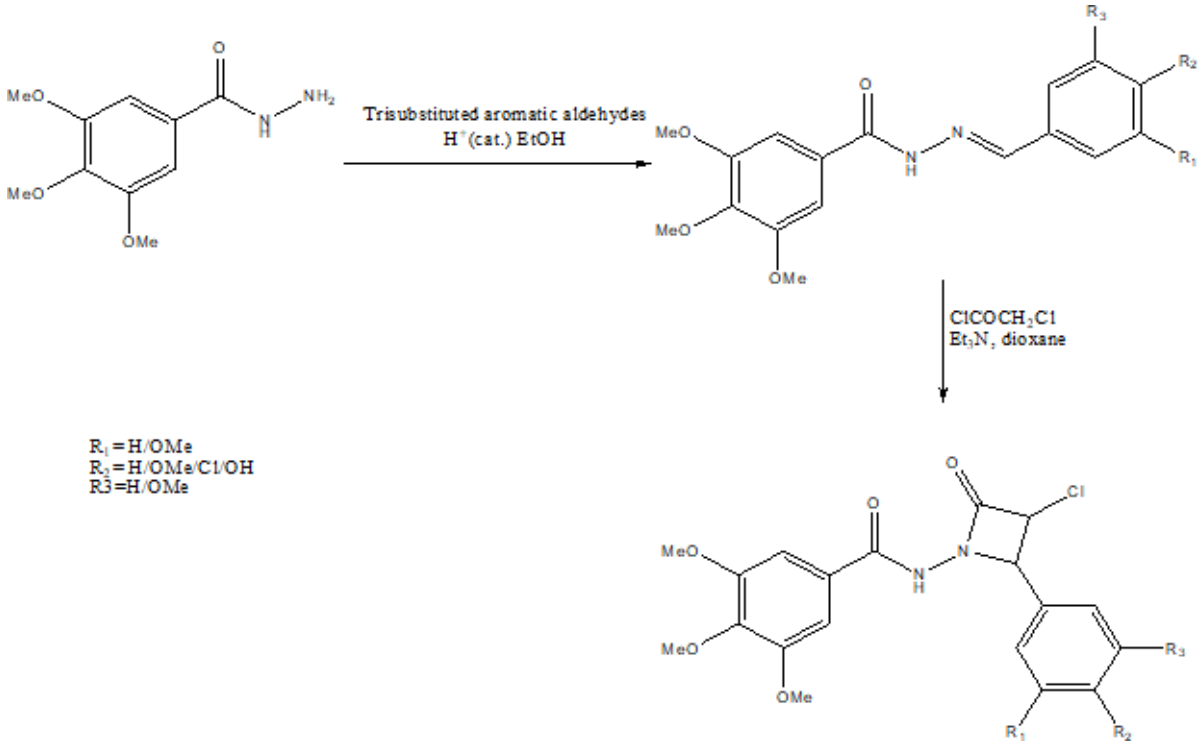



Synthesis of 2- derivatives using substituted hydrazides was proceeded by first treating the hydrzides with aromatic substituted aldehydes in ethanol with acidic condition to prepare Schiff bases. These Schiff bases were then dissolved in diozane then the mixture was sequentially and gradually added with triethylamine and chloroacetyl chloride, then stirred heated to yield 2-azetidinone derivatives as shown in the reaction schemes below by N. B. Ayrim *et al* [15].



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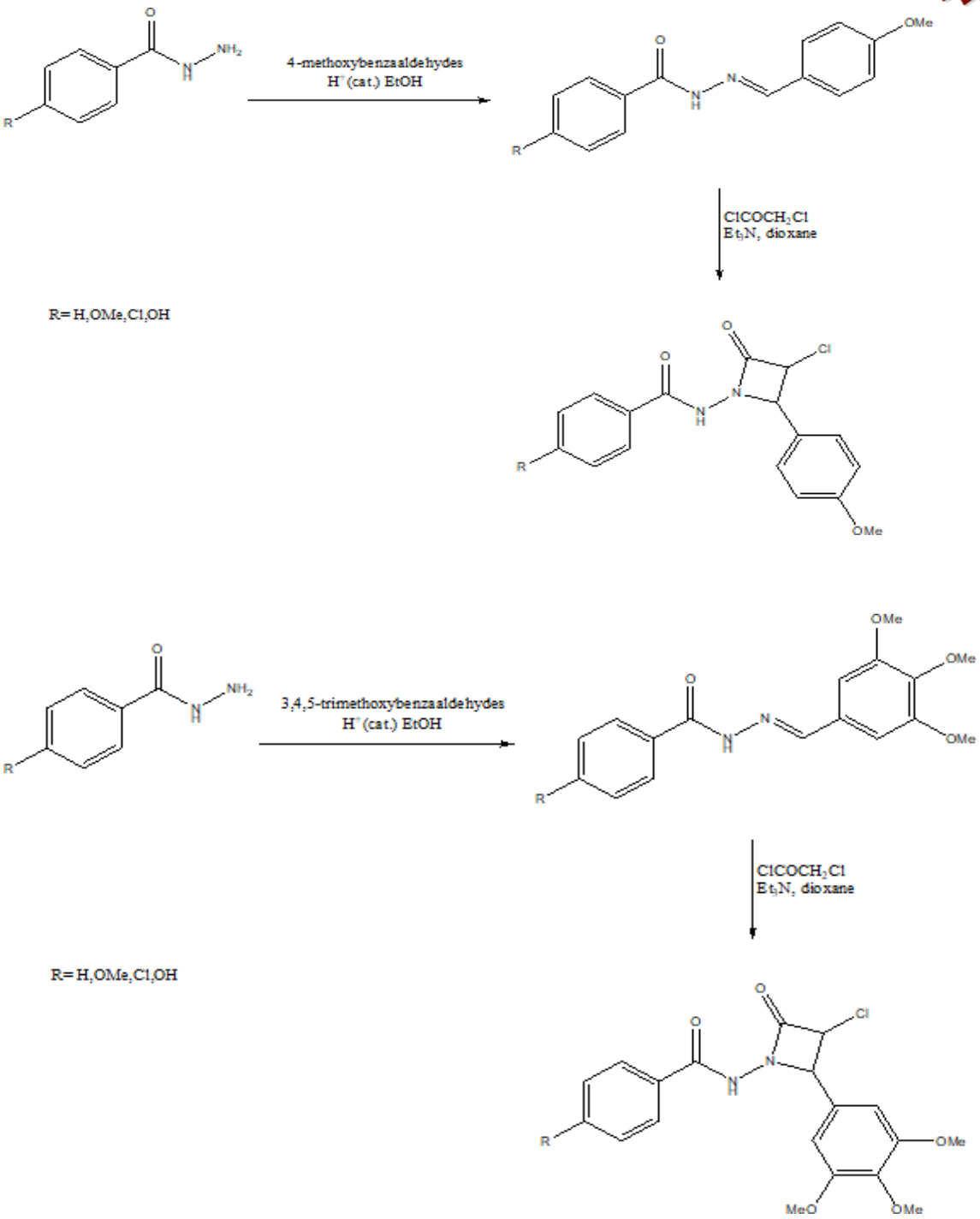


## V.CONCLUSION AND FUTURE WORK

After the detailed literature survey for the synthesis of 2-azetidinone it is concluded that it is one of the most important heterocyclic compounds due to its wide application in the field of medicine, pharmaceutical industry, agricultural sector and organic chemistry. This review can be used as a base to synthesize novel 2-azetidinone derivatives for their application in the above-mentioned fields. This review will help aspiring researchers to choose this moiety for the research purpose to synthesize and study it for its biological activities.

**Conflict of interest**: The author has no conflict of interest.

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**Acknowledgement:**

The author is thankful to the Department of Chemistry, Shri D.M. Burungale Science and Arts College, Shegaon for providing the required facilities to do this literature survey for the review and also thankful to Dr. R. E. Khadsan for his guidance.

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